Deleted in lymphocytic leukemia 2 (DLEU2): An lncRNA with dissimilar

roles in different cancers

Soudeh Ghafouri-Fard[a], Sepideh Dashti[b], Molood Farsi[c], Mohammad Taheri[d,*]

[a] *Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran* [b] *Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran* [c] *Department of Genetics, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran* [d] *Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Deleted in lymphocytic leukemia 2" (DLEU2) is a long non-coding transcript with several splice variants. It has been identified through a comprehensive sequencing of a commonly deleted region in leukemia i.e. the 13q14 region. Afterwards, different investigations reported up-regulation of this long non-coding RNA in several types of cancers. Up-regulation of DLEU2 has been shown to determine poor survival in esophageal, pancreatic, laryngeal, renal, cervical and lung cancers. However, the diagnostic power of DLUE2 has only assessed in two studies; only one them exhibiting promising results. A limitation of most of studies is that they did not differentiate between transcript variants of this lncRNA. Therefore, it is not possible to attribute the observed functions to a certain alternate transcript. In this manuscript, we discuss the results of these studies in three different sections based on the type of experiments.

1. Introduction

Long non-coding RNAs (lncRNAs) have been noticed for their diverse roles in cell survival and apoptosis and their partake in cancers [1]. Among the lately identified lncRNAs with puttaive function in cancer is "Deleted in lymphocytic leukemia 2" (DLEU2). It has been firstly identified through a detailed analysis of chromosome 13q14 region, a genomic area which is frequently deleted in B-cell chronic lymphocytic leukemia (BCLL) [2]. Afterwards, Corcoran et al. comprehensively assessed this genomic region containing this gene, reporting the presewnce of 15 exons in this gene, existence of *RFP2* gene between exons 10 and 12 of *DLEU2* and presence of two microRNA (miRNA) genes in one of its introns [3]. Although the initially identified transcript is though to be a tumor suppressor lncRNA through negative regulation of cell cycle progression [2], a certain alternative transcript of DLUE2 (variant 4, NR_152569.1) has been shown to faciliate cell cycle transition through modulation of expression of angiotensin I converting enzyme 2 (ACE2) and cyclin D1 [4]. DLUE2 has at least seven linear transcript variants. While the longest transcript variant of DLEU2 (NR_152566) has a size of 3092 bp, transcript variant 2 (NR_152567) is 1793 bp long. The transcript variant 4 (NR_152569.1) is the shortest transcript. DLUE2 has also a citcular form being produced through covalent link between 3′ and 5′ terminals [5]. The role of these transcripts in the carcinogenesis has been assessed in a number of investigations. In this manuscript, we discuss the results of these studies in three different sections based on the type of experiments (cell line, animal or clinical experiments).

2. Cell line experiments

Most of studies have shown that up-regulation of DLEU2 increases proliferation, migration and invasion of cancer cell lines. However, there are some exceptions in this regard. For instance, in laryngeal carcinoma cells, forced over-expression of DLEU2 has remarkably decreased proliferation, migration, and invasive properties of cells. Functional studies implied the interaction between DLEU2 and miR-16- 1 suggesting that the anti-oncogenic effects of DLEU2 is possibly exerted through its interplay with this miRNA [6].

Expression of circRNA-DLEU2 has been increased in acute myeloid leukemia (AML) cells. This circular transcript has been shown to enhance proliferation and suppress apoptosis in these cells through its interaction with miR-496 and consequent up-regulation of PRKACB [5]. DLEU2 has been over-expressed in esophageal cancer cells. Small interfering RNA (siRNA)-mediated knock down of DLEU2 has led to

* Corresponding author.
E-mail address: mohammad_823@yahoo.com (M. Taheri).

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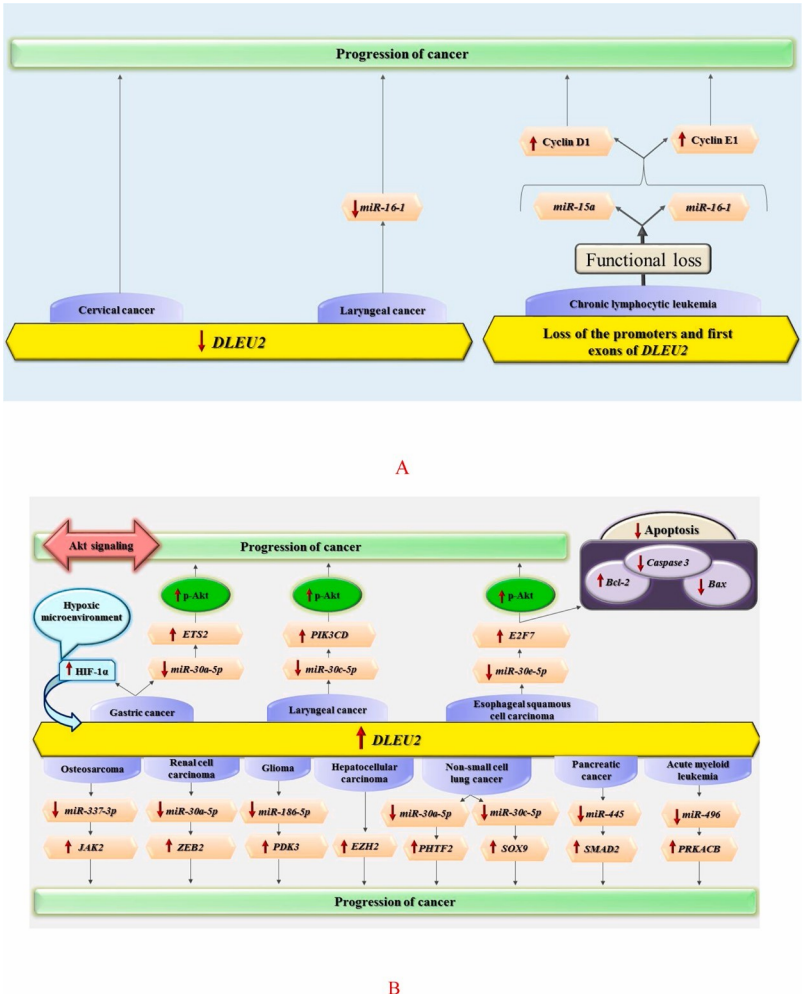

Fig. 1. The role of DLEU2 in the carcinogenesis as a tumor suppressor (A) or oncogene (B). The latter role has been supported by a vast body of literature.

suppression of cell proliferation, migration and invasiveness of these cells, while stimulating cell apoptosis through modulation of the Bcl-2/Bax and Caspase routes. DLUE2 can target miR-30e-5p to increase expression of E2F7 [7]. In gastric cancer cells, DLEU2 silencing has suppressed cell proliferation, migration and invasion, while activating apoptotic processes via releasing miR-30a-5p from its inhibitory effects, thus decreasing ETS2 expression. Notably, hypoxia has led to accretion and nuclear transport of HIF-1α in gastric cancer cells, enhancing expression of DLEU2 [8]. Up-regulation of DLEU2 has also increased proliferation and invasion of pancreatic cancer cell, while its silencing has exerted the opposite effects. miR-455 has been identified as a target for DLUE2, through which this lncRNA controls expression of SMAD2 [9]. DLEU2 silencing in hepatocellular cancer cells has reduced proliferative, migratory and invasive properties of these cell possibly through interference with its interaction with EZH2 [10]. In renal cancer cell, DLEU2 has possibly decreased expression of miR-30a-5p, therefore enhances ZEB2 expression [11]. DLEU2 knock down in non-small cell lung cancer (NSCLC) cells has suppressed the tumorigenesis and invasive ability of these cells. miR-30a-5p has been identified as a target for this lncRNA in NSCLC cells [12]. In glioma cells, DLEU2 has been shown to control expression of PDK3 via a miR-186-5p-dependent route, thus enhancing glioma growth [13]. Fig. 1 summarizes the role of DLEU2 in the carcinogenesis.

Table 1 reviews the investigations which evaluated expression of DLEU2 in cell lines.

3. Animal studies

The results of animal studies are consistent with the oncogenic roles of DLEU2 in cancer cell lines. Different animal models particularly C57BL/6 and BALB/c

mice strains have been used to assess the effects of DLEU2 over-expression or silencing on tumor progression. The results of investigations in xenografts of AML, osteosarcoma, laryngeal cancer, lung cancer and glioma consistently support the pro-oncogenic roles of DLEU2. Ttumor size in mice treated with circRNA-DLEU2-transfected AML cells has been significantly greater than control mice consistent with the over-expression of this circRNAs in the treated animals. Therefore, circRNA-DLEU2 enhances AML-associated tumor development in animal models [5]. Proliferation of tumor cells has also been decreased in animal models transplanted with DLEU2-silenced NSCLC cells. Moreover, this intervention has decreased tumor

Table 1 Summarized results of studies which assessed expression of DLEU2 in cell lines

Cancer type	Targets/ Regulators and Signaling Pathways	Assessed cell lines	Function	Reference
Esophageal squamous cell carcinoma	miR-30e-5p, E2F7, Bcl-2/ Bax axis, Caspase cascade, Akt signaling	Eca-109, KYSE-150, TE-1	↑ DLEU2: ↑ proliferation, ↑ migration, ↑ invasion, ↓ apoptosis	[7]
Gastric cancer	ETS2, miR-30a-5p, AKT signaling miR-30a-5p	AGS, MKN-45	Δ DLEU2: ↓ cell proliferation, ↓ invasion, ↓ EMT, ↓Migration,↑ apoptosis Δ	[8]
		BGC823, MKN-45	DLEU2: ↓ cell proliferation	[14]
	miR-30a-5p	AGS, MKN-28	↑ DLEU2: ↑ proliferation, ↑ invasion	[15]
Pancreatic cancer	miR-455, SMAD2	AsPC-1, PaCa-2, HPDE6-C7	Δ DLEU2: ↓ cell proliferation, ↓ invasion	[9]
Hepatocellular carcinoma	EZH2	SMMC7721, HCLM3	Δ DLEU2: ↓ cell proliferation, ↓ invasion, ↓ migration	[10]
Clear cell renal cell carcinoma	miR-30a-5p, ZEB2	769-P, 786-O, ACHN, Caki-1, HK-2	Δ DLEU2: ↓ cell proliferation, ↓ invasion	[11]
Cervical cancer	–	HeLa, SiHa	↑ DLEU2: ↓proliferation, ↓ colony formation, ↓ migration, ↓ invasion	[16]
Non-small cell lung cancer	miR-30a-5p, PHTF2, PCNA, MMP-2	A549, NCI-H460	Δ DLEU2: ↓proliferation, ↓invasion	[12]
	miR-30c-5p, SOX9	A549, LLC cells	Δ DLEU2: ↓ proliferation, ↓ invasion, ↓ migration, ↑ apoptosis	[17]
Laryngeal cancer	miR-30c-5p, PIK3CD, Akt signaling miR-16-1	Hep2, AMC-HN-8	↑ DLEU2: ↑cell proliferation, ↑ migration, ↑ invasion ↑	[18]
		TU212, A549	DLEU2: ↓cell proliferation, ↓ migration, ↓ invasion	[6]
Osteosarcoma	miR-337-3p, JAK2, JAK2/ STAT3 signaling	Saos-2, NHOst, MG-63, 143B, U-2OS	↑DLEU2: ↑ proliferation, ↑ migration	[19]
Glioma	miR-186-5p, PDK3	U87, U251	↑ DLEU2: ↑ colony formation, ↑ migration, ↑ invasion	[13]
Acute myeloid leukemia (AML)	miR-496, PRKACB	MOLM-13, HL-60, MV-4-11	↑ DLEU2: ↑cell proliferation, ↓ apoptosis	[5]
Chronic lymphocytic leukemia (CLL)	miR-15a/ miR-16-1, Cyclin D1, Cyclin E1	HEK293, P493-6, U2OS, MCF-7	↑ DLEU2: ↓cell proliferation, ↓ colony formation	[20]

Table 2 Summary of studies which assessed function of DLEU2 in animal models (Δ: knock down or deletion).

Cancer type	Animal models	Function and comments	Reference
Acute myeloid leukemia (AML)	Male C57BL/6 mice	↑ DLEU2: ↑ Tumor growth	[5]
Osteosarcoma	Male BALB/c nude mice	↑ DLEU2: ↑ Tumor growth	[19]
Laryngeal cancer	Nude mice	↑ DLEU2: ↑ Tumor growth, ↑ metastasis	[18]
Non-small cell lung cancer	Female BALB/ c-nu mice	Δ DLEU2: ↓ Tumor growth, ↓Tumor	[12]
	Athymic BALB/ c mice	weight Δ DLEU2: ↓ Tumor growth, ↓ metastasis	[17]
Glioma	Female nude mice	Δ DLEU2: ↓ Tumor growth, ↓Tumor weight	[13]

4. Human studies

The majority of human studies have reported up-regulation of DLEU2 in malignant samples. Moreno et al. have detected different DNA methylation pattern at the *DLEU2* locus, including the *miR-15a/16- 1* cluster among patients with AML and healthy subjects. Some probes corresponding to the *DLEU2/Alt1* transcription initiation site have displayed increased levels of methylation in samples from leukemia patients compared with disease-free hematopoietic cells and specimen obtained from those being in remission. However, decreased expression of DLEU2 in leukemic patients has not been associated with expression of mature miR-15a/16-1 [21]. Contrary to its linear form, expression of circRNA-DLEU2 has been increased in AML patients [5]. Assessment of Gene Expression Profiling Interactive Analysis (GEPIA) which provides RNA

The significant over-expression of DLEU2 in the malignant tissues versus benign/ normal tissues also implies applicability of using this lncRNA as diagnostic marker in cancers particularly viability [19]. Table 2 reviews these studies.

in the design of personalized approaches for management of cancers. However, assessment of receiver operating characteristic curves is necessary to obtain

Table 3
Summary of studies reported expression of DLEU2 in clinical samples (overall survival (OS), stomach adenocarcinoma (STAD), Lung adenocarcinoma (LAC), Laryngeal squamous cell carcinoma (LSCC), Esophageal adenocarcinoma (EAD), Pancreatic ductal adenocarcinoma (PDAC), Clear cell renal cell carcinoma (ccRCC)).

Cancer type	Numbers of clinical samples (tissues, Reference	Expression (Tumor vs. Normal)	Transcript variant regression serum, etc.)	Kaplan-Meier analysis Multivariate cox
Esophageal squamous cell carcinoma (ESCC)	96 ESCC cases, 89 EAD cases and 15 adjacent normal tissues	Up	Not mentioned	66 pairs of cancerous and normal tissues
				50 pairs of cancerous and normal tissues
Gastric cancer (GC)		Up	Variant 1 (NR_152566.1)	120 pairs of cancerous and normal tissues
	182 EC tissues and 286 normal tissues	Up	Not mentioned	
		Up	Variant 1 (NR_152566.1)	516 ccRCC patients from the TCGA database FISH analysis: 20 paired LAC tissues qRT-PCR analysis: 15 paired frozen LAC tissues
Osteosarcoma	12 pairs of cancerous and normal tissues			
Pancreatic cancer	GEPIA: 408	Up	Variant 3 (NR_109974.1)	32 pairs of cancerous and normal tissues
	STAD tissues and 211normal tissues	Up	Variant 4 (NR_152569.1), variant 6 (NR_152570.1)	108 pairs of cancerous and normal tissues Microarray
Laryngeal cancer	75 pairs of cancerous and normal tissues	Down	Variant 6 (NR_152570.1), variant 5 (NR_152571.1), variant 1 (NR_152566.1), variant 7 (NR_152572.1), variant 2 (NR_152567.1), NR_002771.1	analysis : 26 pairs of tumor and Over-expression of DLEU2 was associated with poor OS.
		Up	NR_002771.1, variant 1 (NR_152566.1)	
Hepatocellular carcinoma (HCC)	48 pairs of cancerous tissues and para-carcinoma normal tissues	Up	Variant 6 (NR_152570.1), variant 5 (NR_152571.1), variant 1 (NR_152566.1), variant 7 (NR_152572.1), variant 2 (NR_152567.1), NR_002771.1	Increased DLEU2 exon 9 expression had better predictive value than total DLEU2 expression. Patients with high DLEU2 exon 9 expression had worse OS. Over-expression of DLEU2 was associated with poor OS.
Clear cell renal cell carcinoma (ccRCC)	178 pairs of cancerous and normal tissues	Up	Variant 4 (NR_152569.1), variant 6 (NR_152570.1), variant 3 (NR_152568.1), variant 5 (NR_152571.1), variant 7 (NR_152572.1), Variant 2 (NR_152567.1), NR_002771.1	
	laryngeal carcinoma tissue and adjacent non-tumor tissues			– –
		Up	Variant 1 (NR_152566.1)	
Non-small cell lung cancer (NSCLC)			Variant 4 (NR_152569.1), variant 6 (NR_152570.1), variant 3 (NR_152568.1), variant 5 (NR_152571.1), variant 7 (NR_152572.1), Variant 2 (NR_152567.1), NR_002771.1	–
		Up		Over-expression of DLEU2 was associated with poor OS.
Cervical Cancer		Down	Not mentioned	

–	associated with poor OS.			
Over-expression of DLEU2 was associated with poor OS. –	Over-expression of DLEU2 was associated with poor OS.	Over-expression of DLEU2 was associated with poor OS.	Based on GEPIA: Low DLEU2 expression significantly improves OS.	High expression of DLEU2 is an independent prognostic indicator for shorter OS. Increased DLEU2 exon 9 expression is an independent prognostic indicator of shorter OS.	[22]
				–	[7]
				–	[14]
				–	[8]
				–	[19]
				–	[9]
				–	[6]
				DLUE2 expression and tumor stage were independent prognostic factors.	[18]
				–	[10]
				–	[11]
				DLEU2 overexpression was an independent prognostic factor.	[12]

				–		[17]
				–		[16]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	Numbers of clinical samples (tissues, serum, etc.)	Expression (Tumor vs. Normal)	Transcript variant	Kaplan-Meier analysis	Multivariate cox regression	Reference
	adjacent normal tissues					
Glioma	15 glioma tissues and 5 normal brain tissues	Up	Variant 6 (NR_152570.1), variant 5 – (NR_152571.1), variant 1 (NR_152566.1), variant 7 (NR_152572.1), variant 2 (NR_152567.1), NR_002771.1		–	[13]
	TCGA: 163 glioma tissues and 207 normal brain tissues					
Acute myeloid leukemia (AML)	20 AML and 20 healthy samples	Up	Not mentioned	–	–	[5]

Table 4
Diagnostic value of DLEU2 in cancers.

Cancer Type	Numbers of clinical samples	Area Under Curve	Sensitivity (%)	Specificity (%)	Reference
Gastric cancer (GC)	Five paired GC samples and adjacent normal tissues 367 unpaired and 34 paired GC tissue samples from TCGA	0.555	66.67%	45.16 %	[15]
Osteosarcoma	48 pairs of malignant tissues and para-carcinoma normal tissues	0.8021	–	–	[19]
Non-small cell lung cancer	15 pairs of lung adenocarcinoma tissue samples and nearby normal tissues	0.51	81.0%	20.2 %	[12]

the exact sensitivity and specificity values as well as the diagnostic power of DLEU2. Such kind of statistical analysis has been merely performed in the obtained studies. While the results of such kind of application has been promising in the osteosarcoma [19], a single study in NSCLC revealed inappropriateness of DLEU2 as a diagnostic markers. This is because of the low specificity of transcript levels of DLEU2 in distinguishing between NSCLC tissues and non-cancerous tissues [12]. Table 4 gives a brief summary of studies which appraised the diagnostic value of DLEU2 in cancers.

5. Discussion

Up-regulation of DLEU1 has been verified in different malignant samples through both expression analysis of this lncRNA alone and comprehensive expression profiling of lncRNAs. Apart from few studies in some cancers such as cervical cancer and laryngeal carcinoma, the bulk of data from

most cancer types consistently confirm oncogenic roles of this lncRNA. Even in the cervical cancer patients, down-regulation of DLEU2 has been associated with better survival of patients [16]. In vivo studies have been conducted to appraise the effect of ectopic expression or silencing of DLUE2 on tumor behavior. These studies have consistently confirmed the oncogenic impacts of DLUE2.

The locus which encodes the DLEU1 lncRNA also codes for two pro- apoptotic miRNAs, namely miR-15a/16-1. Down-regulation of miR- 15a/16-1 is involved in the enhancement of survival of leukemic cells [23]. Therefore, any aberrations in this locus might affect both the lncRNA and miRNAs, complicating the interpretation of the biological consequences. An important approach in the assessment of expression of DLEU2 is concomitant evaluation of this lncRNA and the related miRNAs hosted by this lncRNA. Such approach has been implemented by Ma et al. They have demonstrated up-regulation of DLEU2, miR-15a and miR-16-1 in esophageal cancer tissues compared with adjacent normal tissues. Yet, expression of mentioned miRNAs have been merely slightly correlated with DLEU2 expression [22].

Another limitation of studies which assessed expression of DLEU2 is that they did not differentiate between two transcript variants of this lncRNA. Therefore, it is not possible to attribute the observed functions to a certain alternate transcript. Ma et al. have reported strong co- expression of the exon 9 of DLEU2 with DLEU2 [22]. Moreover, expression of this exon has been a valuable predictor of survival of patients with esophageal cancer [22], indicating the significance of this exon in the functionality of the cancer-related variant of DLEU2. Future assessment of expression of this exon in various kinds of cancers and appraisal of the correlation between its expression and clinical course of cancer are needed.

DLUE2 has been shown to act as a molecular sponge for various miRNAs to influence their expression (Fig. 2). The interplay between DLUE2 and each miRNA has been recognized in a certain type of cancer. Future investigations are required to find out whether these kinds of interplays are exerted in a tissue-specific manner.

The prognostic impact of DLEU2 has been assessed in a number of human cancers. Up-regulation of DLEU2 has been shown to determine poor survival in esophageal, pancreatic, laryngeal, renal, cervical and lung cancers. However, the diagnostic power of DLUE2 has only assessed in two studies; only one them exhibiting promising results.

Finally, the molecular mechanism of DLEU2 dysregulation in cancer should be verified. The possible mechanisms are abnormal methylation pattern of its adjacent CpG sites and copy number variations.

Collectively, DLEU2 seems to exert oncogenic effects in most tissues, representing a novel target for therapeutic manipulations in cancers. Based on the functional impact of DLEU2 on expression of a number of miRNAs and its subsequent effects on some mRNA coding genes which regulate cell proliferation, such DLUE2/miRNA/mRNA trios are probable targets for this purpose.

Declaration of Competing Interest

The authors report no declarations of interest.

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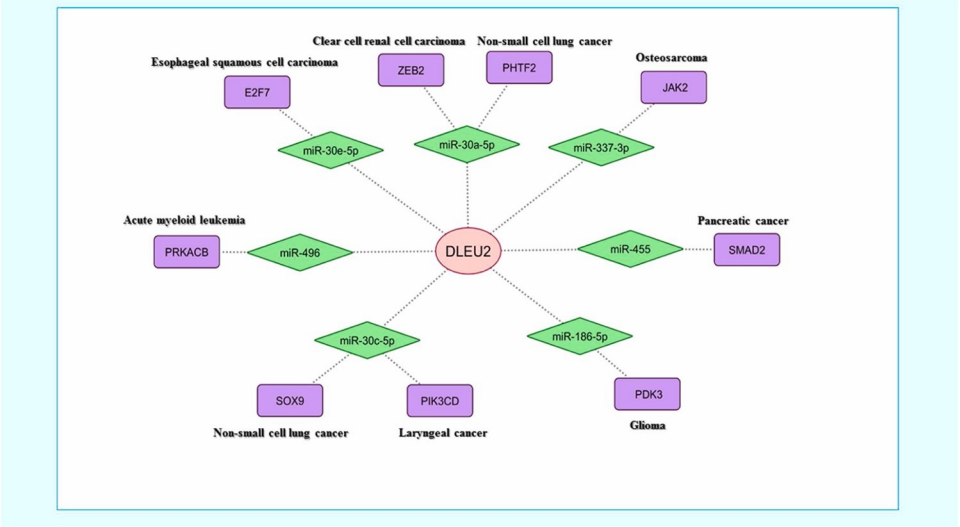

Fig. 2. DLEU2 acts as a molecular sponge for a number of miRNAs.

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